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Evaluation of OnabotulinumtoxinA Treatment in Patients with Concomitant Chronic Migraine and Temporomandibular Disorders

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ABSTRACT

Introduction: Migraine and temporomandibular disorders (TMD) are both common diseases and TMD are reported as a risk factor in migraine progression. OnabotulinumtoxinA is used in the treatment of chronic migraine (CM), and also has a potential role in TMD treatment. In this study, it is aimed to compare the efficacy of onabotulinumtoxinA treatment in CM patients with and without TMD.

Methods: In this retrospective study, 30 CM patients (age range: 18–65 years), satisfying the inclusion and follow-up criteria in their medical records were investigated. The PREEMPT injection protocol was taken as reference and onabotulinumtoxinA 155–195 U with fixed-dose has been administered into 31 specific sites within the head/neck muscles in included subjects. Two cycles of treatment were assessed in all patients at the baseline and 12 weeks later. The headache diaries, which were completed routinely one month before, and during 6 months follow-up after the treatment, were assessed. The effect of onabotulinumtoxinA treatment was compared between CM patients with and without TMD/bruxism.

Results: Of 30 female patients, 17 had concomitant TMD. In week 24, there were significant improvement in the groups with and without TMD regarding to the mean change of frequencies in the days with migraine compared to the initial findings ($p<0.001$). However, there was no significant difference between the two groups.

Conclusions: OnabotulinumtoxinA is an effective and safe treatment for CM. Its efficacy appears to be similar in CM patients with and without TM, speculating that the comorbidity of TMD did not play a role for the treatment response.

Keywords: Temporomandibular disorders, headache, onabotulinumtoxinA, chronic migraine

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INTRODUCTION

Chronic migraine (CM) is a debilitating neurological problem that affects 1.3% to 2.4% of the general population (1–4) and also represents 7.7% of the total migraine population (5). The diagnosis of CM in clinical practice has been made according to the Revised International Classification of Headache Disorders-2 (ICHD-2R) (6).

A group of disorders involving the temporomandibular joints and masticatory muscles or both and causing pain and dysfunction is defined as temporomandibular disorders (TMD) (7, 8). The annual incidence rate of TMD in the population is 6.5% (9). The prevalence of TMD and migraine is higher in females than males, and also higher in young and middle-aged adults compared to the elderly. The prevalence rates of TMD peak in patients aged 25 to 44 years (10% of men and 18% of women) (10).

The higher prevalence of TMD symptoms in migraine patients compared to patients with episodic tension-type headache forms the basis for the hypothesis that TMD and migraine are comorbid conditions (11). TMD are more common in female migraineurs compared to women without headache (12). Besides, migraine was reported to be the most common primary headache type in patients with TMD (13). The prevalence of TMD symptoms in subjects with and without headache was found to be 27.4% and 15.2%, respectively (14). This intriguing relationship between migraine and TMD is not clearly defined. In addition, there is limited evidence to support the theory that TMD are a risk factor for high migraine frequency, and for onset of CM (13, 15–19).

The use of botulinum toxin in patients with migraine and neck disorders (cervical dystonia-related, whiplash-associated neck pain) for palliation of pain underlies its potential use in the management of TMD (20–23). Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials revealed that onabotulinumtoxinA had higher efficacy for decreasing headache days with migraine compared to placebo (24–26).

The phenotype of migraine patients with TMD may represent the aggregated contribution of both disorders leading to chronification. In clinical practice, separate treatment is given for each component

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in the patients having CM and TMD. Moreover, TMD are usually under-recognized in patients with CM. The role of treatment with onabotulinumtoxinA has not been studied in these patients. Therefore, in this study it is aimed to retrospectively evaluate the efficacy of onabotulinumtoxinA treatment in patients with CM and concomitant TMD, in comparison to CM patients without TMD to give an insight to pain specialists for the treatment of these groups of patients.

METHODS

Study Design

All medical records were retrospectively screened to find those patients a) who were treated at least for two cycles with onabotulinumtoxinA with the diagnosis of CM, and b) had been examined for concomitant TMD between March 2012 and January 2013 in two neighbor university-based headache outpatient clinics. Both clinics were sending their CM patients to the same dentistry clinics for evaluation of TMD as a part of their routine management protocol. As the strict reimbursement protocol from the social health security was closely related with the full documentation of the onabotulinumtoxinA procedure, the patients were followed meticulously by pain diaries after and before injections, routinely. Due to this formal and standardized process, we are able to obtain a good dataset and this retrospective study was designed meticulously.

Patients

All patients with the diagnosis of TMD and CM, treated with onabotulinumtoxinA with available detailed follow-up findings were included. We compared onabotulinumtoxinA treated CM patients with TMD to those without TMD. The CM cohort was aged 18 to 65 years. If the patients took prophylactic treatment for migraine before enrollment, this treatment schedule was continued just the same during the onabotulinumtoxinA treatment, in our routine management protocol. If the patients had started any migraine prophylaxis within the previous 3 months prior to start of their own baseline period, they were excluded to prevent a biased treatment effect. The patients who suffered from medication-overuse headache according to the criteria proposed by the ICHD-2R, were included in the current study, only if they had a successful washout period of one month documented in their files. All participants gave written informed consent, and the retrospective study protocol was approved by the Institutional Ethics Committee (No: 2015/42).

Migraine Diagnosis and Evaluation

A senior neurologist with expertise in headache management evaluated all potential participants. CM was defined according to the ICHD-2R and included following criteria: 1) days of headache ≥15 days in a month, present for at least 3 months, 2) at least eight days of migraine-headache (out of 15 days) without aura and/or responsive to migraine-specific treatments, and 3) headache not associated with different etiology and medication overuse (6).

Cutaneous Allodynia Questionnaire (CAQ) (27), Beck Depression Inventory (BDI), Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1), and Migraine Disability Assessment scales (MIDAS) (Turkish version) had been performed in all participants before the first injection according to our routine management protocol. The symptoms of cutaneous allodynia were evaluated using the CAQ, already adapted and validated in Turkish (27). MSQ v2.1 is composed of 14 questions evaluating the limitations due to migraine in daily performance (28). A value is obtained by summing the scores calculated from the questionnaire. Migraine-related disability was evaluated using the Turkish version (29) of the Migraine Disability Assessment scales (MIDAS) (30).

All patients were already trained to use headache diaries and they recorded the headache frequency, duration and severity of migraine attacks, number of moderate/severe headache days, number of total headache hours on headache days, besides use of acute medication, during the study periods. The severity of headache was classified as mild, moderate, or severe in the diary records. The patients with missing data in all these parameters were excluded from the study.

Assessment of Temporomandibular Disorders

All patients with CM were asked six questions written below to screen the presence of TMD by the neurologists. In case of positive answer to one of the questions, the patients were referred and evaluated by a specialized oral surgeon in maxillofacial surgery and temporomandibular junction to determine whether actual TMD were present. The participants who gave no positive answer to the questions were used as a control group in the study. The questions asked to the patients were as follows:

1. Is there any limitation (≥40 mm) in the mandibular movements?
2. Is there any pain during mouth opening?
3. Is there any sound during mandibular movement? If yes, is it like "click" or "crepitation"?
4. Is there any locking at the joint? If there is locking, is it associated with pain or not?
5. Is there any sliding in the lower jaw during mouth opening?
6. Are there any grinding teeth (bruxism)?

Clinical trials on TMD took The Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) into account for diagnostic tool reference (31). Due to the limited number of patients, the criteria of RDC/TMD Axis I was used to grouping the TMD such as myofascial pain, disk displacement. The "limited opening" and "crepitation" items of as Axis I questionnaire were specifically asked. Patients were examined clinically and asked also for the following symptoms: joint and facial muscle pain, joint noise, bruxism, painless maximum mouth opening, cervical and shoulder muscle pain, headache frequency and severity and global head and neck pain. The symptoms of the patients were graded from moderate to severe prior to onabotulinumtoxinA treatment. Treated patients were examined for palliation of symptoms every four weeks. The patients underwent panoramic radiography (9 patients), and open and closed-mouth magnetic resonance imaging (7 patients) to support the clinical diagnosis by an experienced radiologist.

Injection Protocol

Fixed-dose of onabotulinumtoxinA (Botox®) 155 U was injected to 31 fixed-site in 7 specific head/neck muscle regions according to the PREEMPT injection protocol. Additional dose of 2x20 U was administered to each masseter muscle using a "follow-the-pain" strategy. The patients were injected at baseline and 3 months later. The dose scheme and results of this trial are specific to the formulation of Botox®. At month 3, second Botox® 195 U was administered according to the same protocol.

Study Period

We adopted a 28-day baseline screening phase and a 24-week follow up phase assessing available headache diaries related with 2 injection cycles. Only the data of patients who are able to fulfill their diary and with suitable symptoms for ICHD-2R criteria were investigated. As the next step, CM patients were evaluated whether they had TMD. Afterwards, these CM patients were divided into TMD and control groups without TMD for our study purposes. The follow up of the patients were arranged at regular periods during 6 months by the same neurologists to evaluate headache diaries and adverse effects. The examination of temporomandibular joint was also performed by the same experienced oral surgeon in maxillofacial surgery and temporomandibular junction in the İstanbul Faculty of Dentistry.

Statistical Analysis

The headache diaries and data collected for 4 weeks before injection were considered as basal data. The effect of onabotulinumtoxinA treatment was compared between CM patients with and without concomitant TMD. Statistical analysis was performed with SPSS 16.0 (IBM, Somers, NY, U. S. A.) using descriptive analyses. Wilcoxon signed-rank test was used to calculate the mean change of the scores from baseline within the treatment groups. Mann-Whitney U test was used to calculate the significance of changed scores between groups. Student's t-test was used to compare the sample means and chi-square test to compare the categorical data. A value of $p<0.05$ was considered statistically significant for all tests.

RESULTS

Demographics and Baseline Headache Characteristics

A total of 32 patients with a diagnosis of CM who had all necessary information according to our selection criteria were included in this retrospective study. All patients were females. Two of the patients had deteriorated during the follow up. Reevaluation of these two patients with lumbar puncture revealed the diagnosis of intracranial hypertension without papilledema, and these patients were excluded from further analysis despite fulfilling the inclusion criteria. Out of 30 remaining patients, 17 were diagnosed to have concomitant TMD, 7 of them supported with magnetic resonance imaging findings. No significant difference regarding to demographic characteristics was found between the groups (Table 1).

Efficacy results

A remarkable mean decrease in frequency of headache days from baseline was observed in both treatment groups at initial post-treatment visit (week 4) and week 24 (-9.9 days with TMD; p=0.001 vs -10.5 days without TMD; p=0.004) (Fig. 1). On the other hand, there was no significant difference between the groups.

Significant reductions were observed for the following efficacy parameters: mean change for frequencies of migraine days from initial (with TMD group p=0.001; without TMD group p=0.004); moderate or severe headache days (with TMD group p=0.001; without TMD group p=0.005); cumulative headache hours on headache days (with and without TMD group p=0.002); headache episodes (with TMD group p=0.001; without TMD group p=0.013) and migraine episodes (with TMD group p=0.001; without TMD group p=0.016) in both treatment groups at the first post-treatment study visit (week 4) and including the week 24 visit (Figs 2. a–e). Again there was no significant difference between the groups (Table 2).

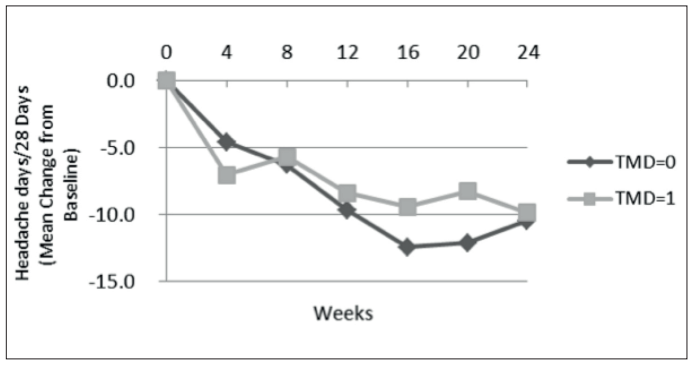

Figure 1. Mean change from baseline in frequency of headache days. Headache days at baseline: 20.6±4.7 with TMD group versus 20.6±4.9 without TMD group, p=0.885. All data are presented as means (TMD=0: Chronic migraine without temporomandibular disorders, TMD=1: Chronic migraine with temporomandibular disorders).

Table 1. Baseline demographics and characteristics of the study groups

	CM with TMD (n=17)	CM without TMD (n=13)	p value
Mean age, years	34.94	30.08	0.114
Female, %	100	100	
Mean BMI	24.82	25.17	0.854
Mean disease duration, years	16.91	11.92	0.175
Mean headache days (SD)	20.59 (4.73)	20.85 (4.86)	0.885
Mean migraine days (SD)	17.59 (5.86)	15.69 (6.06)	0.394
Mean headache episodes (SD)	18.82 (6.01)	19.08 (7.10)	0.917
Mean migraine episodes (SD)	15.88 (6.52)	14.08 (6.86)	0.468
Mean moderate/severe headache days (SD)	16.53 (6.21)	14.23 (4.87)	0.281
Mean cumulative hours of headache occurring on headache days (SD)	233.53 (120.28)	231.92 (108.62)	0.970
Past prophylaxis	65% (11/17)	39% (5/13)	
Present prophylaxis	47% (8/17)	15% (2/13)	
Mean CAQ score[a]	9.41	10.31	0.609
Mean MIDAS score[b]	20.59	19.92	0.822
Mean MSQ v2.1 score[c]	46.47	47.46	0.777
Mean BDI score[d]	21.00	18.62	0.537

[a]CAQ: Cutaneous Allodynia Questionnaire; scores of 0–2 indicate no allodynia; 3–5 mild; 6–8 moderate; 9 or higher severe
[b]MIDAS: Migraine Disability Assessment scales; scores of 0–5 indicate Grade 1 (little or no disability); 6–10 Grade 2 (mild disability); 11–20 Grade 3 (moderate disability); ≥21 Grade 4 (severe disability)
[c]MSQ: Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1)
[d]BDI: Beck Depression Inventory; scores of 0–9 indicate minimal depression; 10–18 mild depression; 19–29 moderate depression; 30–63 severe depression

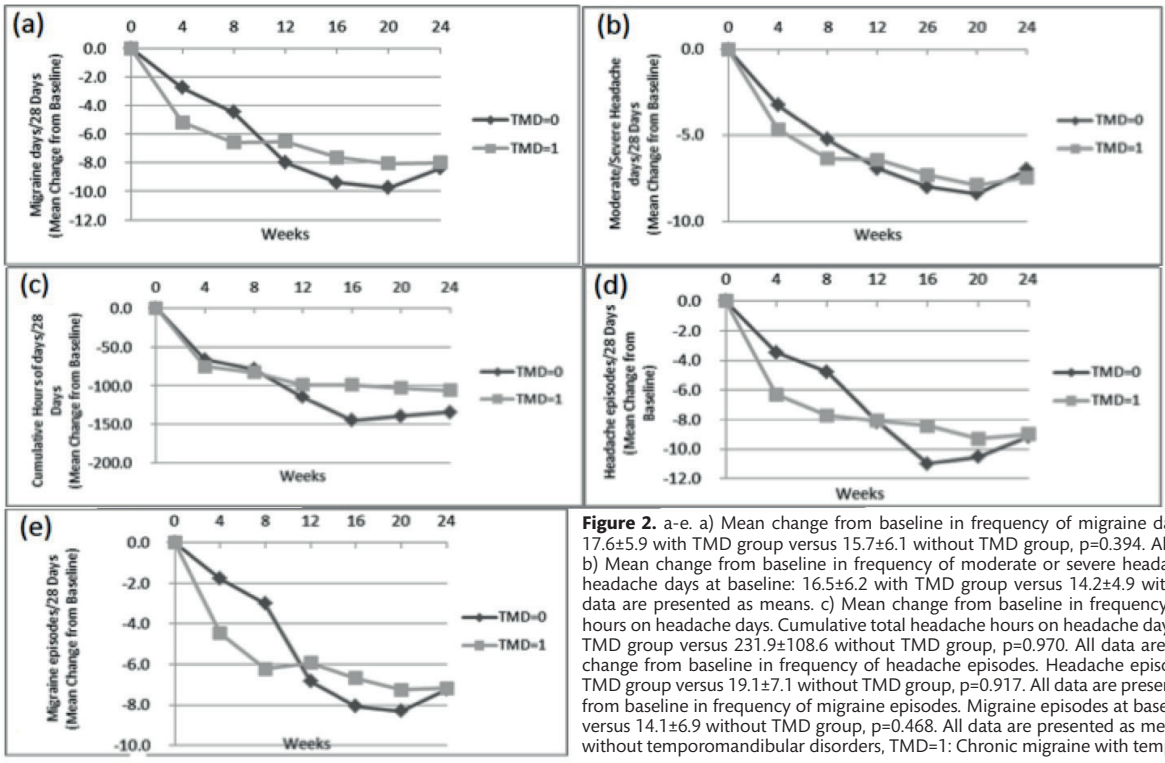

Figure 2. a-e. a) Mean change from baseline in frequency of migraine days. Migraine days at baseline: 17.6±5.9 with TMD group versus 15.7±6.1 without TMD group, p=0.394. All data are presented as means. b) Mean change from baseline in frequency of moderate or severe headache days. Moderate or severe headache days at baseline: 16.5±6.2 with TMD group versus 14.2±4.9 without TMD group, p=0.281. All data are presented as means. c) Mean change from baseline in frequency of cumulative total headache hours on headache days. Cumulative total headache hours on headache days at baseline: 233.5±120.3 with TMD group versus 231.9±108.6 without TMD group, p=0.970. All data are presented as means. d) Mean change from baseline in frequency of headache episodes. Headache episodes at baseline: 18.8±6.0 with TMD group versus 19.1±7.1 without TMD group, p=0.917. All data are presented as means. e) Mean change from baseline in frequency of migraine episodes. Migraine episodes at baseline: 15.9±6.5 with TMD group versus 14.1±6.9 without TMD group, p=0.468. All data are presented as means (TMD=0: Chronic migraine without temporomandibular disorders, TMD=1: Chronic migraine with temporomandibular disorders).

Out of these 17 patients with CM and concomitant TMD, 9 had also completed their follow-up visits during the 24 weeks in the dentistry clinics for the assessment of their TMD. The responses of their symptoms to the treatment were shown in the Table 3. These 9 CM patients with concomitant TMD had no statistically significant differences compared to all group regarding the response of headache parameters to onabotulinumtoxinA treatment.

Safety and Tolerability

The adverse events (AEs) were similar for both groups with or without TMD. The incidence of total treatment-related adverse effect was 41% (7/17) in the group with TMD and 61.5% (8/13) in the control group. Total treatment-related AEs were shown in Table 4. There was no serious adverse effect. The most common AEs were neck pain and eyebrow elevation. Most of the AEs were of mild or moderate severity and disappeared without any sequelae. None of the patients reported muscular weakness, eyelid ptosis and musculoskeletal stiffness. Only

Table 2. Efficacy of OnabotulinumtoxinA at week 24

	CM with TMD (n=17)	CM without TMD (n=13)	p value
Change from baseline in frequency of headache days (%)	-9.9 (-50.2)	-10.5 (-50.2)	0.836
Change from baseline in frequency of migraine days (%)	-8.0 (-53.4)	-8.4 (-45.3)	0.880
Change from baseline in frequency of moderate/severe headache days (%)	-7.4 (-49.2)	-7.0 (-45.2)	0.838
Change from baseline in cumulative total headache hours on headache days (%)	-105.6 (-58.0)	-134.5 (-47.0)	0.525
Change from baseline in frequency of headache episodes (%)	-9.0 (-47.9)	-9.2 (-50.9)	0.961
Change from baseline in frequency of migraine episodes (%)	-7.2 (-51.4)	-7.2 (-45.7)	0.988

Table 3. Efficacy of OnabotulinumtoxinA treatment on patients with TMD, followed up in the dentistry clinic

Patient	Age	Joint Pain	Joint Noise	Mouth opening	Bruxism	Headache
1	30	+	+	+	++	+
2	41	-	+	+	-	+
3	25	+	+	+	-	+
4	42	+	+	same	+	+
5	20	+	+	+	+	+
6	29	+	+	+	+	+
7	29	++	same	++	++	+
8	59	+	+	+	+	+
9	38	+	+	+	+	+

+; improvement, ++; prominent improvement

Table 4. Total treatment-related adverse events

	CM with TMD (n=17); n (%)	CM without TMD (n=13); n (%)
Total treatment related adverse events	7 (41)	8 (61.5)
Neck pain	1 (5.8)	3 (23)
Eyebrow elevation	2 (12)	1 (7.7)
Injection-site pain	1 (5.8)	1 (7.7)
Difficulty chewing	1 (5.8)	1 (7.7)
Jaw pain	1 (5.8)	1 (7.7)
Myalgia	1 (5.8)	1 (7.7)

CM: Chronic migraine, TMD: Temporomandibular disorders

one patient from the TMD group discontinued the treatment due to AE; namely due to eyebrow elevation.

DISCUSSION

The PREEMPT trial showed that onabotulinumtoxinA is safe, well-tolerated and effective in the prophylaxis of CM (24–26, 32). Thus, onabotulinumtoxinA is specifically indicated only for the prophylaxis of CM headaches (33). However, the determinants of a favorable response to this expensive injection therapy are not clearly elucidated. Following approvals in other countries, onabotulinumtoxinA was also approved for the treatment of CM in our country after 2011 (34), and became a routine part of the management of CM patients in headache centers. In this retrospective study, onabotulinumtoxinA treatment resulted in significant improvements in headache days and multiple headache symptom measures; number of migraine days, number of moderate and severe headache days, total headache hours on headache days, number of migraine and headache attacks in treatment groups during the study, consistent with the literature (24–26, 32) irrespective of the presence of concomitant TMD, as shown for the first time in this study.

Botulinum toxin with its muscle-relaxing effect, is also suggested to have a potential role in the treatment of TMD (20–23). It inhibits release of acetylcholine from the presynaptic vesicles in the neuromuscular junction irreversibly and the additive action was hypothesized to include the blocking of release of the neurotransmitters including substance P glutamate, and calcitonin gene-related peptide and impact on muscle spasm and nerve transduction (35, 36). Local muscle paralysis can not fully explain the pain reliever characteristic. Although the exact mechanism for elucidating the physiology of onabotulinumtoxinA in prophylaxis of CM is not well-known, inhibition of neurotransmitters related with pain transmission is hypothesized as a responsible mechanism based on human and animal studies (35, 37–39). It was postulated that transmission of signals from peripheral to central nervous system is blocked by inhibiting release of neurotransmitters from peripheral termini of primary afferents (35, 37, 40) and central sensitization is inhibited. Besides this, a recent study demonstrated that onabotulinumtoxinA selectively inhibited C- but not Ad-trigeminal meningeal nociceptors by utilizing a preclinical cranial pain model (41). With respect to this study application of onabotulinumtoxinA on cranial surface blocks mechanical transduction in meningeal pain receptors and prevention of fusion of mechano-sensitive ion channels into the nerve terminal membrane by onabotulinumtoxinA underlies its prophylactic effect in CM treatment (41).

In the era of minimally invasive dentistry, onabotulinumtoxinA plays an important role and provides a new option for the treatment of a number of dental problems but mostly without a clear clinical evidence (42). Intramuscular injections of onabotulinumtoxinA with mechanisms of providing symmetric action of muscles; reduce pain, decrease the masseter hypertrophy and result in normal function of temporomandibular joints. The patients in this study with the diagnosis of CM and concomitant TMD reported a decrease in temporomandibular junction pain and noise, and the majority of responding patients also reported a decrease in myalgia and headache after onabotulinumtoxinA treatment (Table 3). Our results support the potential role of onabotulinumtoxinA in TMD treatment, and onabotulinumtoxinA may be suggested as a minimal invasive therapeutic option for non-responders to traditional treatments of TMD.

There were debates and different views for the definition and criteria of CM for a long time; hence CM is possibly one of the areas neglected in the first classifications of migraine, and could not take the place it deserves in the studies, for long years. The continuing debates about CM include, if it is different from other chronic daily headaches or it is an evolutionary form of episodic migraine, or a completely different disease (43). Elucidation of these points is only possible after uncovering the unknown mechanisms of CM (43). The higher frequency of migraine attacks is closely related with the higher probability of development of CM. Patients with 5–9 days of migraine attacks a month has a 6-fold higher risk to develop CM compared to patients having <4 days of migraine attacks a month (44). Obesity, stress, snoring, depression, medication overuse, migraine progression (increased frequency and severity of migraine attacks) are known as modifiable risk parameters for CM (5, 45). Cutaneous allodynia was identified as increased central sensitization and an independent predictor for migraine chronification (46). The prevalence of allodynia was higher in patients with CM, and directly proportional to migraine duration and the number of attacks (46). Moreover, it was reported that a range of other pain disorders coexisted with migraine and with TMD, based on limited evidence (14, 15, 47–49).

TMD may be one of the determinants of the onabotulinumtoxinA response in CM. TMD may relate with the etiologic mechanism of headache for the following potential reasons: TMD may result in headache, a secondary disorder as classified in the ICHD-II (6) TMD may increase the severity of existing primary headache disorder. TMD-induced mechanical dysfunctions (repetitive stimuli caused by bruxism and gripping teeth, associated with myogenic pain from the masticatory muscles) lead to release of serotonin and norepinephrine from the dorsal raphe and locus ceruleus, with an activation of a cascade of events (50). Antecedent headache, such as migraine, may get worse and increase muscle stress (50). As a result, the comorbidity of migraine and TMD may be present, and the final phenotype is formed by their negative additive effect on each other. This study showed that TMD are highly prevalent (17/30) among patients with CM consistent with the literature but their comorbid presence did not seem to indicate a different phenotype of CM in relation to allodynia reflecting central sensitization or quality of life and disability created by migraine, besides migraine days and other related migraine parameters as seen in Table 1.

People with migraine and TMD show more allodynia than those with migraine without TMD (51). These patients also have severe allodynia (mean CAQ score is >9 in both treatment arms) in the current study. On the other hand, no significant difference was found between treatment arms. At the beginning, it was hypothesized that the presence of TMD could be one of the possible predictors of a positive response, so this hypothesis was tested retrospectively in a well-established database. However, the results did not support this, and showed that TMD did not play a role for the treatment response.

There is only one study in the literature that investigated the effectiveness of isolated and/or concomitant treatments of both migraine and TMD (52). In that study, combination treatment did reach statistical significance versus the other three treatment groups (propranolol alone, stabilization

splint therapy alone, or placebo) in the intention-to-treat sample (52). But this study had an entirely different methodology and patient population (not with CM); therefore, the current results could not be compared with its results, although being partly supportive for showing the independence of the treatment responses of these comorbid conditions.

The current study has some limitations: The sample size of well-documented patients was small and all of them were females. The inability of performing power analysis a priori due to this limited number of patients could be accepted as a weakness of this manuscript, which is the first retrospective study evaluating the role of comorbid TMD.

CONCLUSION

In evaluated CM patients, either with or without TMD, onabotulinumtoxinA came out as an effective prophylactic treatment, and resulted in significant improvements, besides being safe and well tolerated. The results study showed that TMD are highly prevalent among patients with CM but their presence did not seem to indicate a different phenotype of CM, and the comorbidity of TMD did not play a role for the treatment response. Thus, TMD seem to be only an "innocent bystander" in that aspect. Although being retrospective, this is the first study of the evaluation of onabotulinumtoxinA treatment for CM and concomitant TMD in the literature. However, more evidence and further randomized prospective clinical studies should be conducted to find better combination treatments for CM and TMD.

Ethics Committee Approval: The retrospective study protocol was approved by the Institutional Ethics Committee (Istanbul Medical Faculty Ethics Committee) (No: 2015/42)

Informed Consent: All participants gave written informed consent.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - YG; Design - YG GK, BBB; Supervision - YG, BBB, BGK; Resource - YG, GK, BBB; Materials - GK, NK, ZM, BB; Data Collection and/ or Processing - GK, NK, ZM, BB; Analysis and/or Interpretation - YG, GK, BBB; Literature Search - GK, BBB; Writing - GK, BBB; Critical Reviews - YG, BBB, BGK, ME.

Conflict of Interest: The authors declare that there is no conflict of interest.

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